PATENT
Docket No.: 19603/3232 (CRF D-2587B)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Goldman et al.	Examiner: Q. Nguyen
Serial No.	:	09/846,588	Art Unit: 1636
Cnfrm. No.	:	4784	
Filed	:	May 1, 2001	
For	:	METHOD OF INDUCING NEURONAL PRODUCTION IN THE BRAIN AND SPINAL CORD	

DECLARATION OF M. FLINT BEAL, M.D. UNDER 37 C.F.R. §1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, M. FLINT BEAL M.D., pursuant to 37 C.F.R. § 1.132, declare:

1. I received a B.A. degree in Biology from Colgate University in 1972 and an M.D. degree from University of Virginia in 1976.

2. I am the Anne Paris Titzell Professor and Chairman of Neurobiology at Cornell University Medical College, New York, N.Y. and Neurologist-in-Chief at The New York and Presbyterian Hospital, New York, N.Y.

3. It is my understanding that the present invention is assigned to Cornell Research Foundation, Inc., a subsidiary of Cornell University.

4. As demonstrated in my Curriculum Vitae (attached hereto at Exhibit 1), I have extensive expertise in the area of neurodegenerative diseases and their treatment, including Huntington's Disease. In particular, my areas of research have included the discovery and evaluation of new pharmacological treatment approaches for Huntington's Disease as well as for related neurodegenerative diseases, in particular, amyotrophic lateral sclerosis.

5. I have reviewed the Declaration of Steven A. Goldman under 37 C.F.R. § 1.132, the Second Declaration of Steven A. Goldman under 37 C.F.R. § 1.132, and the Third Declaration of Steven A. Goldman, M.D., Ph.D. Under 37 C.F.R. § 1.132 for the above patent application and am providing this declaration to explain the significance of the present invention.

6. Drs. Goldman and Benraiss found that viral overexpression of brain-derived neurotrophic factor ("BDNF") in the normal adult rodent ventricular system induces the generation of new neurons from the neural stem cell population of the ventricular subependyma. The new neurons migrate to the olfactory bulb primarily, but a large cohort invades the striatum as well, where they integrate as new striatal neurons. These cells adopt a DARPP32/GABAergic/calbindin+ phenotype, characteristic of the medium spiny neuronal population of the caudate-putamen. This is the predominant neostriatal phenotype lost in Huntington's Disease; as such, Drs. Goldman and Benraiss postulated that the induced generation of this cell type might be a feasible strategy for slowing or reversing disease progression. In an effort to increase the numbers of neurons generated through this approach, Drs. Goldman and Benraiss found that the numbers of new neurons recruited to the striatum in response to BDNF were increased by concurrently suppressing subependymal gliogenesis, using adenoviral overexpression of noggin protein. Used together, BDNF and noggin over-expression induced the addition of over 350 new neurons/mm^3/month to the adult rodent neostriatum. This effect is pronounced in both normal mice and rats, and in mouse transgenic models of Huntington's Disease. The new neurons largely assume medium spiny neuronal phenotype, and project to the globus pallidus. These cells are generated in sufficiently high numbers, over a long enough period of time, and with sufficiently robust maturation, survival, and network integration, that they were able to improve deficient striatal function in the R6-2 mouse model of Huntington's Disease ("HD"). Drs. Goldman and Benraiss found that when co-injected with both AdBDNF and AdNoggin intraventricularly, the HD mutant mice exhibited a significant delay in disease progression, sustained motor performance, and prolonged survival relative to untreated and null-virus treated controls. In broad terms, these findings indicate that induced neurogenesis may be viewed as a potential therapeutic modality for HD. Specifically, BDNF overexpression is necessary and sufficient to permits the generation in the adult brain of new striatal neurons of the identical phenotype lost in HD. Furthermore, the addition of noggin augments the numbers of these BDNF-induced neurons, so as to provide a feasible and effective treatment approach to

HD. As such, these experiments lay both a conceptual and operational foundation for the BDNF and BDNF/noggin-mediated induction of striatal neurogenesis as a therapeutic strategy in HD.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 12/06/04

M. Flint Beal

M. Flint Beal, M.D.